PATENT
Docket No. 559662000101

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Dated: December 16, 2005 Signature: Marian L. Christopher (Marian L. Christopher)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of:

Bruce J. ROSER

Serial No.: 09/888,734

Filing Date: June 25, 2001

For: DRIED BLOOD FACTOR COMPOSITION COMPRISING TREHALOSE

Examiner: Francisco Chandler Prats

Group Art Unit: 1651

REPLY BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This responds to the Examiner's Answer mailed 18 October 2005 setting a non-extendable date to respond to 18 December 2005.

A Request for Oral Hearing is attached to this reply.

Introduction

Appellant appreciates the concurrence of the Examiner with §§ 1-6 and 8-9 of the Appeal Brief. The issues focus on the validity of the grounds for rejection argued in § 7.

There are two grounds for rejection – one of claims 14-16 over Curtis (U.S. patent 5,824,780) in view of Livesey, *et al.* (U.S. patent 5,364,756) and rejection of claims 14-16 and 20-22 over a combination of these documents with Bhattacharva, *et al.* (U.S. 5,288,853). Appellant will not argue the latter basis for rejection separately; both grounds for rejection fail, in Appellant's view, because the combination of Curtis and Livesey neither teaches nor suggests the invention claimed in claims 14-16 from which claims 20-22 depend.

Claim 14, the only independent claim, is directed to a method which has a number of elements:

1. The method uses, as a substrate, native Factor VIII. It does not use activated Factor VIII which has been altered structurally by treatment with thrombin.

2. A stabilizing amount of trehalose must be present.

3. A stabilizing amount of albumin must be absent.

4. The active step is that of freeze-drying.

5. The subject of freeze-drying must be an aliquot of aqueous solution of native Factor VIII (containing trehalose and free of albumin).

Specific Responses to the Examiner's Answer

The claimed invention is not simply about the use of trehalose as a cryoprotectant. Appellant is well aware that trehalose is a commonly used cryoprotectant. The reason Appellant has spelled out so specifically all of the claim limitations is to emphasize that this is not about trehalose.

A. The Absence of Albumin

A critical limitation in the claims, as recognized, is the requirement that albumin be absent. In Appellant's view, the Examiner has not given sufficient weight to the knowledge

common in the art and made of record early on in prosecution that it was generally accepted that albumin was required in order to stabilize preparations of Factor VIII, whether prepared from plasma or recombinantly produced. The evidence of record has been included with the Appeal Brief behind tab 5. Attention is called, for example, to Exhibit 2, a description of Factor VIII in the Physicians' Desk Reference (PDR) which specifically states in its description of recombinant Factor VIII, "the final preparation is stabilized with albumin (human) and lyophilized." Exhibit B is an article appearing in 2001 describing clotting Factors VIII and IX; on page 82, it is noted that recombinant Factor VIII "was stabilized by the addition of human albumin" (lines 3 and 4). A subsequent paragraph, also on page 82, notes that the B-domainless recombinant Factor VIII (analogous to the activated form) is formulated without the addition of human albumin, which is cited as an advantage. This, of course, emphasizes the substantial irrelevance of the Curtis document that is concerned exclusively with activated Factor VIII. A general discussion of the need for albumin as a stabilizer in Factor VIII compositions is provided in Exhibit C, WO 94/07510 at the top of page 3, "human albumin functions as a general stabilizer during purification, sterile manufacturing and freeze-drying (see review by Wang, *et al.* . . .)."

The point is that the requirement for the absence of albumin must be viewed in the context of the art-understood knowledge that albumin was required to stabilize Factor VIII – a point that appears to be ignored by the Examiner in evaluating the teachings of both Livesey and Curtis. Neither document specifically suggests that trehalose might be used to overcome the requirement for albumin in the stabilization of Factor VIII in a world where Factor VIII is known to require albumin for stabilization.

As to Curtis, even in the context of activated Factor VIII (analogous to that free of the B-domain noted above) there is no teaching that trehalose should be used during freeze-drying to

obviate a requirement for, or generally in the absence of, albumin. The only mention of stabilizers is in column 5, lines 39-42, which notes that the *activated* Factor VIII can be lyophilized and stored and notes that stabilizers that might be used at various points in the process (not necessarily specifically with regard to freeze-drying) include albumin, sucrose, maltose, glycine and trehalose. There is no suggestion in this listing that trehalose can be used instead of albumin or in the absence of it. Albumin is specifically included on the list of stabilizers consistent with the knowledge of the art. The discussion quoted by the Examiner from Livesey in column 9, beginning at line 16, describes various cryoprotectants and combinations thereof. The combination of human serum albumin plus trehalose is specifically suggested at line 38 (not bolded in the quotation set forth in the Examiner's Answer). And since the description quoted in column 9, lines 16-39, is generic to all of the materials to be subjected to Livesey's process, any conclusion that trehalose is suggested to be used alone as a substitute for albumin in the context of Factor VIII specifically is simply not there.

Livesey purports to extend its disclosure to a great variety of products, as can be seen from column 4, lines 57-64. The disclosure of cryoprotectants and dry protectants at column 9, lines 5-39, must be viewed in this context – it is a long list of materials that *might* be suitable for the particular biological material that the reader is interested in. Livesey does not promise that, say, DMSO (col. 9, l. 6) is suitable for use with sperm (col. 4, l. 61) or that sucrose (col. 9, l. 29) will be suitable for preserving platelets (col. 4, l. 60). Similarly, Livesey does not teach the reader that trehalose, on its own and without albumin, can be used to stabilize Factor VIII. The reader with an interest in formulating Factor VIII would bring his background knowledge to Livesey and, if he thought that there was any correlation between the list of substances in column 9 and the list of biological products in column 4, would probably think that the

disclosure of "human serum albumin plus trehalose" at column 9, line 38, was the one that was relevant to Factor VIII. It is inconceivable that Livesey, which contains no biological data concerning Factor VIII, would induce the person skilled in the art to jettison his belief that albumin was required in order to stabilize Factor VIII.

One might consider an analogous situation in which the invention is made up of parts fixed to each other. The specification might state that the parts can be made of wood (for example balsa wood), metal, plastics (for example polyethylene), etc., and another part of the specification might state that the parts can be fixed to each other by a variety of means, for example nails, screws, aqueous adhesives, solvent-based adhesives, etc. The reader skilled in the mechanical arts, who knows that screws cannot be used to affix balsa wood parts to each other and certain solvent-based adhesives cannot be used to affix polyethylene parts to each other, would not seize on that specification as suddenly informing him that, actually, screws can be used for balsa wood and those solvent-based adhesives can be used for polyethylene.

It may be significant that the Examiner repeatedly refers to the claims of Livesey; see the Examiner's Answer at page 4 (last paragraph) and pages 11 and 12. The claims are not the primary source of technical information for the reader; they are present in order to define the scope of legal protection afforded by the earlier patent. Furthermore, claims 13-22 simply represent the same shopping list as at column 4, lines 60-64, split into different claims, so the Examiner's focus on claim 17, as being specifically directed to Factor VIII, is misplaced. The recitation of Factor VIII in Livesey's claim 17 does not cause the reader to focus on Factor VIII any more than the list in column 4.

Furthermore, claim 17 is not dependent on claim 9, so the Examiner's attempts on page 12 and in the passage bridging pages 13 and 14 of the Answer to draw together the

"vitrification solution" of claim 9 and the Factor VIII of claim 17 fails. There is nothing in Livesey to suggest to the reader that any of the solutions of claim 9 would be suitable for Factor VIII. They are disclosed only for preserving whole cells; see Examples 1 and 4 of Livesey.

Thus, neither Curtis nor Livesey teaches anything related to the invention except that trehalose can be included on a list of cryoprotectants for activated Factor VIII (Curtis) or for biological suspensions in general (Livesey). There is nothing in either document that trumps the well-established principle that the use of albumin to stabilize Factor VIII preparations was considered essential in the art at the time the application herein was effectively filed (January 19, 1995). To date, apparently, other than as described in the present invention, only the activated form of Factor VIII has been formulated without albumin. This is noted in Exhibit D (also behind tab 5) in a document dated 10 October 2000. The second full paragraph indicates that although up until then, it was required to include albumin in preparations of Factor VIII, a new product, Kogenate® FS is stabilized only by sucrose. Page 3 of Exhibit A (also behind tab 5) states that the earlier Kogenate® product was formulated with pasteurized human serum albumin, as approved by the FDA in 1993. Thus, the desirability of eliminating albumin was/is recognized, but this was not achieved prior to the present invention.*

Thus, the record clearly indicates that "native," *i.e.*, unactivated Factor VIII, was considered, at the effective date of filing, always to require albumin as a stabilizing agent. None of the description quoted by the Examiner from Curtis or Livesey even suggests eliminating albumin from activated Factor VIII, much less native Factor VIII.

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* This is verified also by the declaration of Dr. Francis Preston, attached hereto. This was filed with the Response submitted 25 September 2002 and inadvertently omitted from the Evidence Appendix attached to the Appeal Brief.

B. Native Factor VIII vs. Activated Factor VIII

The Examiner disputes the characterization of activated Factor VIII as being substantially different from, and therefore not informative concerning, native Factor VIII. This is directly contradictory to the testimony of two experts in the field, one of whom (Helgerson) is the co-inventor on the Curtis document. Paragraph 3 of Dr. Helgerson's declaration clearly states that the teachings in the patent which he co-authored are inapplicable to native Factor VIII. This view is endorsed by the testimony of Dr. Tuddenham in paragraphs 4 and 5 of his declaration:

> Thus, even if Curtis showed that the activated form of Factor VIII which itself has cofactor activity could be stably preserved in the presence of trehalose, there is no scientific basis to extrapolate this to the native Factor VIII which lacks such cofactor activity until proteolytically cleaved by thrombin. It simply does not follow.

And further:

> In my opinion the activated form of Factor VIII and the native form of Factor VIII (as a circulating heterodimer) are sufficiently different that the physical behavior of one is not predictive of the physical behavior of the other.

There is no objective evidence submitted by the Examiner to contradict the sworn testimony of these experts in the field.[†] Essentially they have testified that any teachings of Curtis regarding activated Factor VIII are irrelevant to methods regarding native Factor VIII. And, as noted above, at best, Curtis simply teaches that trehalose can be included in a laundry list of cryoprotectants, a fact not denied by Appellant.

On pages 7 and 8 the Examiner considers that it is "unfair" to characterize the native and activated forms of Factor VIII as being very different, and points out that the proteins possess numerous virtually identical amino acid sequences. It is true that much of the three separate

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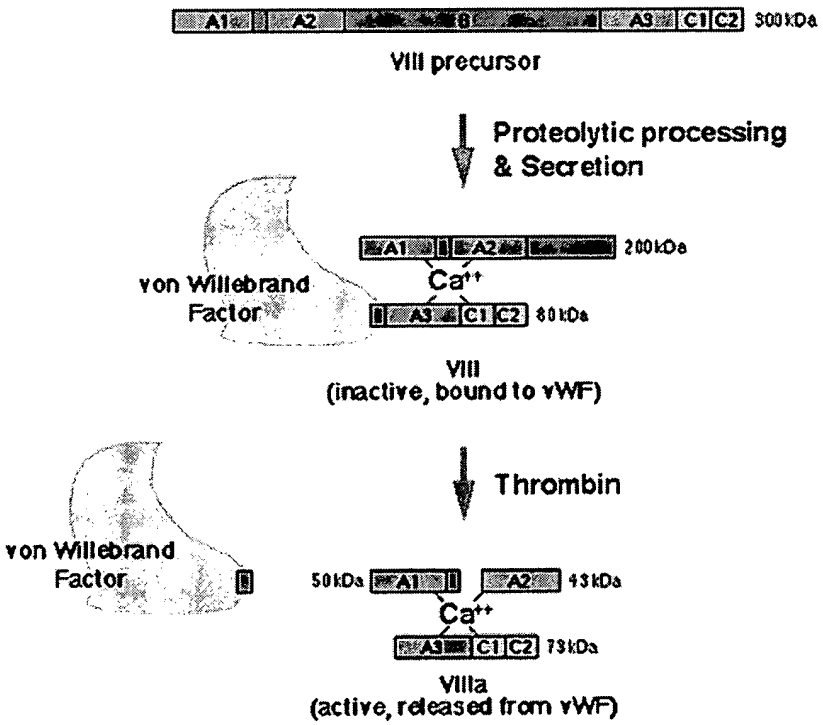
[†] Dr. Preston's declaration verifies this as well.

sequences of activated Factor VIII can be found in native Factor VIII. However, a large section of native Factor VIII is absent in activated Factor VIII. Changing even one amino acid in a protein can change its properties sufficiently to cause diseases such as sickle cell anemia and cystic fibrosis. Similarly, the solubility and other physical properties of insulins can be changed markedly by altering just one amino acid in the protein. It is clear that one cannot simply assume that what was taught for activated Factor VIII can be applied to native Factor VIII (which contains a whole extra domain of some 980 amino acids), as shown in the diagram below of the activation of Factor VIII *in vivo*, where the native Factor VIII is designated "VIII precursor."



C. Aliquots of Solution vs. Nebulized Suspensions

The Examiner also overlooks the thrust of the teaching of Livesey, *et al.,* (forming a nebulized preparation) and the fact that Livesey does not teach any process at all for freeze-

drying an aliquot of an aqueous solution of anything. This was discussed in detail on page 9 of the Appeal Brief, and Appellant finds nothing in the Examiner's Answer to rebut the description that only bulk suspensions are appropriate for Livesey's process, not aliquots of solution. The general statement that "an aliquot of aqueous solution is broad enough" to cover a process where a bulk suspension is nebulized and rapidly cooled to obtain an amorphous phase of water, cubic ice crystals and hexagonal crystals as well as a suspension of the biological material does not seem adequate to address the arguments made by Appellant.

An "aliquot" is a measured volume of a liquid that, on its own, is suitable for a defined use, such as analysis or delivery to a patient. The term does not encompass a single spray-dried microdroplet as in Livesey, which would simply be too small to be useful on its own. When preparing Factor VIII (or any other therapeutic protein) in measured doses for ultimate administration to a patient, there is no way that the solution would be spray-dried from a bulk solution, since it would then be impossible, under appropriate conditions, to distribute the dried particles into vials, each containing the same dose of Factor VIII. No person skilled in the art of formulating Factor VIII would regard the Livesey disclosure as being remotely relevant or useful. The term "aliquot" is an important feature of the claim, which reflects the manufacturing process for Factor VIII compositions in their final packaging. It cannot be equated to a microdroplet or the resulting dried particle.

In designing a process for preparing a stabilized Factor VIII composition, the person skilled in the art would clearly need to bear in mind the need to operate the process aseptically. In a process that involves nebulizing a bulk solution/suspension, the thus-formed powder would need to be split up into individually-weighed portion for placing into each final container. It is not feasible for this to be done aseptically on a manufacturing scale and thus the person skilled in

the art would not start down that road. It is notable that Livesey's Examples 1 to 4 involve whole cells, which do not need to be divided into doses. In Example 5, although the nebulized product is divided into vials, the product in question is an *oral* polio vaccine, which is not subject to the same stringent requirements concerning sterility and precise dosage as an injected therapeutic product such as Factor VIII.

The defects in Example 5 of Livesey as a paradigm for the procedure claimed in the present application have been discussed extensively in the Appeal Brief, and Appellant believes no further discussion is required here except to point out that for oral polio vaccine suspensions (as exemplified), nothing that was done with them short of destroying the attenuated poliovirus could ever form an aliquot of an aqueous solution. The reader will not be misled, if the overall disclosure is considered, into thinking that a "cryosolution of a suspension of biological material" refers to a homogeneous mixture which overall is considered a solution. This is at least evident from the examples wherein the "cryosolutions" clearly contain suspensions of biological materials. Further, the nature of the "cryosolution" is described in column 3 which specifically states that the "cryosolution" includes "a suspension of the biological material."

The Examiner misleadingly refers to Example 5 of Livesey as being the "lone example of protein freeze-drying of Livesey" (Examiner's Answer, page 5). Example 5 does not relate to protein freeze-drying, in the sense of an isolated protein such as Factor VIII (which is the sense in which the Examiner is using the term). Rather, it relates to whole live viruses, namely those that make up oral polio vaccine.

In sum, Livesey, and Example 5 in particular, is directed to a specific process and does not describe freeze-drying of biological materials in solution, and certainly not in aliquotted form.

D. Motivation to Combine

In light of the clear testimony of Drs. Helgerson and Tuddenham that the behavior of activated Factor VIII with regard to stabilization, etc., cannot be extrapolated to Factor VIII itself, there is no motivation to combine Curtis with Livesey. The only motivation provided by the Examiner is, apparently, that both list trehalose in laundry lists of cryoprotectants. As noted above, the ability of trehalose to act as a cryoprotectant in general is not at issue here. What is at issue is a specific process for preparing a stable native Factor VIII composition which is a combination of multiple elements of which trehalose is only one.

E. Conclusion

Livesey and Curtis, even combined, fail to suggest the method of the invention. The combination clearly does not suggest subjecting native Factor VIII to freeze-drying in the absence of albumin, although the art available at the time teaches that this is a necessary element in stabilizing Factor VIII. The combination of documents also fails to suggest freeze-drying an aliquot of an aqueous solution of native Factor VIII. In addition, there is no valid rationale for combining these documents since one concerns the properties of activated Factor VIII, clearly distinguishable from native Factor VIII as attested by two recognized experts, and the other is concerned with 'freeze-drying' a nebulized suspension of biological particles which merely mentions Factor VIII on a laundry list (inappropriately). The two documents are not related by any suggestion contained within them to make the combination or with any commonality of the problem to be solved. Certainly neither is such a high profile document that everyone in the art would be aware of it. It is not even clear, after the fact, why the combination has been made since the combination fails to teach the invention as claimed.

In light of the foregoing, Appellant again requests that the rejections be withdrawn and claims 14-16 and 20-22 be passed to issue.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to **Deposit Account No. 03-1952**.

Respectfully submitted,

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enclosures:

declaration of Dr. Francis Preston, attached hereto.

A Request for Oral Hearing is attached to this reply.